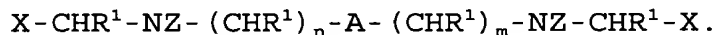


## R E M A R K S

### Interview

Counsel wishes to extend thanks to Examiners Chapman and Wu for granting the interview of June 6, 1995. At the interview, counsel and the examiners discussed the possibility of providing comparative test results. At the conclusion of the interview, Examiner Chapman indicated that the desired comparison would be between compounds of applicants' formula I and compounds of Berg et al. (EP '795 or U.S. '208). This conclusion was reached because the Berg et al. disclosure, like applicants' claims, is directed to MRI imaging. The Berg et al. reference is also the primary reference in the rejection of all of the claims under 35 U.S.C. §103.

Berg et al. disclose chelate agents for production of chelate compounds that can be used in magnetic resonance imaging. Chelating agents of the formula



The  $R^1$  groups are defined as "a hydrogen atom, hydroxy alkyl group, or an optionally hydroxylated alkoxy or alkoxyalkyl group."

Meares et al. (U.S. '420), which was also discussed at the interview, discloses chelating agents. However, the use of chelate complexes as MRI contrast agents is not described. The chelating agents of U.S. '420 are analogs that are useful as bifunctional chelating agents that can be attached to biological molecules. Claim 1 of U.S. '240 recites optically active and substantially optically pure chelating agents that are ethylenediaminetetraacetic acid (EDTA), ethylenediaminetriacetic acid (ED3A) and diethylenetriaminepentaacetic acid (DTPA) analogs. In the analogs, the ethylene moiety is substituted at one carbon atom by an R substituent selected from, *inter alia*,  $-CH_2-\Phi$ ,  $-CH_2-\Phi-OH$  and  $-CH_2-\Phi-OCH_3$ , wherein  $\Phi$  presumably represents a phenyl group.

Although applicants appreciate the guidance provided by Examiners Chapman and Wu with respect to comparative experiments,

reconsideration of the rejections under §112 and §103 is respectfully requested.

**Rejection under 35 U.S.C. §112, fourth paragraph**

Claim 14 is amended above to depend from independent claim 11 rather than cancelled claim 12. In addition, claim 33 is amended to be in independent form rather than dependent upon cancelled claim 1. In view of the above, withdrawal of the rejection under 35 U.S.C. §112, fourth paragraph, is respectfully requested.

**Rejection under 35 U.S.C. §112, second paragraph**

The rejection under §112, second paragraph, assumes that claim 33 is dependent from claim 11. As amended above, claim 33 is an independent claim. Withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

**Rejection under 35 U.S.C. §103:**  
**Berg et al. in view of Gries et al.**

**(a) Berg et al.**

As mentioned above, Berg et al. (EP 0 299 795 and U.S. 5,198,208) disclose a genus of aminopolycarboxylic acids, as well as their use as MRI contrast agents. See formula I at column 2, lines 1-45, and the reference to MRI contrast agents and diagnosis at column 17, lines 21-31, and column 18, lines 26-33.

In this genus of compounds, the pendant  $R_1$  groups are defined as being "hydrogen atom, a hydroxyalkyl group, or an optionally hydroxylated alkoxy or alkoxyalkyl group." See column 2, lines 26-28. Specific examples of the  $R_1$  groups are disclosed at column 3, lines 16-22.

In the examples of U.S. '208, the compounds of Examples 1 and 2 do not exhibit pendant  $R_1$  groups, i.e.,  $R_1$  is H. Examples 3, 5, 22-26, 29-33, 37 and 38 exhibit a cyclic base structure, rather than a linear structure. In Example 4, the compound has a single pendant  $R_1$  group which is hydroxyethyl. See also Examples 9, 10 and 41. The compound of Example 21 is similar to that

of Example 4, except that the sole pendant  $R_1$  group is hydroxymethyl rather than hydroxyethyl.

In the compounds of Examples 6, 7, 8, 36 and 40, there are two pendant  $R_1$  groups per compound. In each case, the pendant  $R_1$  groups are hydroxymethyl.

Examples 11-20 use chelating compounds described in the prior examples. Examples 27, 28, 34 and 35 use the chelating compound of Example 6. Finally, in Example 39, the compound prepared exhibits one pendant  $R_1$  group, i.e., 5,6-dihydroxy-3-oxa-hexyl.

It is evident from the examples and the disclosure bridging columns 2 and 3 that the focus of Berg et al. is directed to chelating compounds and chelate complexes having a linear base structure and a hydroxylated pendant group, in particular hydroxylated alkyl or hydroxylated alkoxyalkyl. Nothing within the disclosure provides any suggestion to modify such pendant structures.

Neither U.S. '208 or its EP counterpart provides any suggestion that would lead one of ordinary skill in the art to a pendant group in accordance with applicants'  $Z^1$  and  $Z^2$  groups. See, for example, the proviso clause of claim 11 which recites that the group  $-(O)_r-R$  in the  $Z^1$  or  $Z^2$  group is not OH.

**(b) Gries et al.**

Gries et al. (EP 0 263 059) lists German applications DE 36 33 245 and DE 36 33 246 for purposes of priority. These two German patent applications are also cited for priority purposes in U.S. patent application Serial No. 07/614,947 (pending) which is a continuation of Serial No. 07/494,803 (abandoned) which, in turn, is a continuation of Serial No. 07/100,681 (abandoned). The latter two patent applications are also listed in the family history of Radüchel et al. (U.S. 5,399,340).

EP '059 discloses a genus of compounds that can be used in MRI diagnostics. See page 2, lines 29-33, as well as the genus of compounds described by formula I at page 2, line 35-page 3, line 10. The compounds of formula I exhibit at least one amide structure defined by the group  $-CH_2CO-NR^3R^4$ . In addition, the

linear base structure exhibits pendant groups  $R^1$  and  $R^2$  which are hydrogen atoms, lower alkyl groups, phenyl groups or benzyl groups. At page 3, lines 33-35, EP '059 lists examples of alkyl radicals for groups  $R^1$  and  $R^2$ . In the compounds disclosed in the examples of EP '059, there are no pendant groups, i.e.,  $R^1$  and  $R^2$  in each case is H.

**(c) Combination**

In the rejection, it is argued that EP '059 discloses an equivalence between alkyl groups, phenyl groups and benzyl groups. If, for the sake of argument, such equivalence can be gleaned from the disclosure of EP '059, that equivalence is only relevant to the amide complexes of formula I of EP '059. The disclosure of EP '059 provides no hint of an extrapolation that such pendant groups would be equivalent in all chelating compounds or chelate complexes.

Moreover, absent from the disclosure of EP '059 is any teaching as to alkoxy, phenoxy or benzyloxy pendant groups. One of ordinary skill in the art would recognize that alkyl and alkoxy are different groups. Nothing within the prior art of record suggests any equivalence between alkyl and alkoxy as pendant groups of compounds with linear base structures when used as MRI contrast agents. An allegation of equivalence between alkyl and, e.g., phenyl groups does not translate into a teaching of any equivalence between alkoxy groups and other groups.

The rejection argues that it would be obvious to modify an alkoxy group by focusing not on the entire group but only on its alkyl portion. In particular, the rejection asserts that it would be obvious to modify pendant alkoxy groups within the compounds of Berg et al. by substituting a phenyl or benzyl portion for the alkyl portion to arrive at benzyloxy or phenoxy group. However, neither Gries et al. nor Berg et al. provide any suggestion of benzyloxy or phenoxy groups. Even the alleged equivalency disclosed by Gries et al. is solely in the context of alkyl, phenyl and benzyl groups.

Motivation is a requirement for obviousness under 35 U.S.C. §103. Such motivation must be derived from the prior art disclo-

tures or the art in general. The needed motivation cannot come from applicants' disclosure and/or hindsight construction.

If one ignores applicants' claimed invention for the moment, an analysis of the prior art disclosures clearly leads one in another direction. As discussed above, the focus of the Berg et al. disclosure is on hydroxylated groups. Although it is disclosed that the pendant R<sup>1</sup> groups can, for example, be alkoxy, the R<sup>1</sup> groups of all of the compounds in the preparation examples are hydroxylated. Thus, while generically, alkoxy groups are encompassed, the clear focus of the teaching is toward hydroxylated pendant groups.

On the other hand, Gries et al. generically disclose pendant groups for their amide compounds which are alkyl, phenyl or benzyl. Yet, none of the specific compounds disclosed by EP '059 exhibit any pendant groups, i.e., R<sup>1</sup> and R<sup>2</sup> are each H.

The mere ability, in and of itself, to modify the disclosure of a reference or to combine two or more references together does not establish obviousness under 35 U.S.C. §103. See In re Lasowski, 10 U.S.P.Q.2d 1397 (Fed. Cir. 1989); and In re Gardner, 177 U.S.P.Q. 396 (C.C.P.A. 1973). Instead, there must be some motivation which would lead one of ordinary skill in the art to make the alleged modification.

As can be seen from the above discussion, U.S. '208 mentions certain alkoxyated and/or hydroxylated pendant groups. On the other hand, the specifically disclosed compounds of EP '059 possess no pendant groups. Neither reference discloses benzyloxy or phenoxy pendant groups. Nor do they disclose that a phenyl structure is equivalent with the alkyl portion of a group such as alkoxy when that group is pendant off a linear base structure in a chelating compound/chelating complex.

It is respectfully submitted that, when these two disclosures are combined, there is no motivation which would lead one of ordinary skill in the art to a benzyloxy or phenoxy containing pendant group in accordance applicants' Z<sup>1</sup> or Z<sup>2</sup> structure.

(d) Ex parte Koster

In the rejection, reference is made to the 1961 decision by the Patent Office Board of Appeals in Ex parte Koster, 136 U.S.P.Q. 75. Based on this decision, it is argued that benzyl-oxy, phenoxy and alkoxy groups are equivalent structures.

In Koster, the genus of certain borazane compounds of the formula  $H_3B:NR_1R_2R_3$ . In the claimed invention,  $R_1$ ,  $R_2$  and  $R_3$  groups were hydrocarbon groups. In the compound of claim 16, two were methyl groups and the third was cyclohexyl. In claim 17, two were methyl groups and the third was phenyl. In claim 23, the three hydrocarbon groups were defined as saturated lower alkyl, saturated cyclo lower alkyl and phenyl radicals, with at least one of the radicals being cyclo lower alkyl or phenyl.

These claims were rejected based on a reference that described similar compounds wherein all of the hydrocarbon groups were alkyl groups and the total carbon atoms within these alkyl groups was 4-12. In maintaining the rejection, the Board stated: "[s]aturated cyclo lower alkyl and phenyl radicals are so extremely common that we believe that any chemist of ordinary competence would readily realize that said radicals might be substituted for one of the alkyl radicals of Brown's compounds."

The Board's decision is made in the context of Brown's compounds, i.e., the compounds of the prior art reference which were trihydrocarbon borazane, like those being claimed by Koster. The Board does not make a *per se* rule that in all cases, regardless of the class of compounds, their structure or their use, a phenyl radical or cycloalkyl radical is always, without exception, an equivalent of an alkyl radical.

For example, if one of ordinary skill in the art were presented with the Berg et al. disclosure which involves chelate complexes for use as contrast agents in NMR and X-ray diagnostics, and Koster's disclosure of trihydrocarbon borazanes that individual would be provided no suggestion to take the pendant structures described by Berg et al. and substitute other structures therefor. Nor would there be any suggestion to isolate a portion of those pendant and modify that portion. Koster's

compounds are not chelates and they do not exhibit an alkylene-amine base structure, with or without pendant groups.

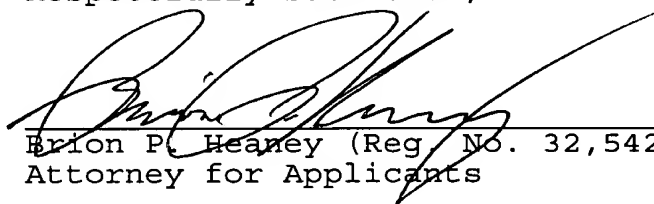
Furthermore, the Koster decision does not state, in all cases or any cases, that alkyl and alkoxy are equivalent or that phenoxy/benzyloxy is an equivalent of alkyl.

In view of the above remarks, it is submitted that U.S. '208 (or EP '795), taken alone or in combination with EP '059, fails to provide sufficient motivation which would lead one of ordinary skill in the art to modify the disclosure of U.S. '208 in such a manner as to arrive at applicants' claimed invention. Withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

**Rejection under 35 U.S.C. §103:  
Gries et al. in view of Lauffer**

This rejection is rendered moot by the cancellation of claims 33-35. Claims 33-35 are cancelled solely to further prosecution and are not to be construed as an acquiescence to any ground of rejection.

Respectfully submitted,



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